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Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients

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Background: The increased incidence of malignancies in patients with chronic renal failure has been discussed since the mid-70s. On the other hand, the high frequency of chronic renal insufficiency among cancer patients has been recently assessed in the Insuffisance Rénale et Médicaments Anticancéreux Study which demonstrated a prevalence as high as 50%–60% of the patients for all stages of kidney disease. Furthermore, the incidence of end-stage renal disease is growing worldwide and so is the number of patients on chronic dialysis, hemodialysis (HD) for the large majority of them. As a result, the question of cytotoxic drug handling in those patients in terms of dosage adjustment and time of administration regarding the dialysis sessions needs to be addressed to optimize cytotoxic drug therapy in those patients.
Methods: We reviewed the international literature on the pharmacokinetics, efficacy, tolerance and dosage adjustment of cytotoxic drugs used to treat solid tumor patients and when available, specific literature on HD cancer patients.
Results: From these data, dosing recommendations are given for the most prescribed cytotoxic drugs in clinical practice.
Conclusions: Dosage adjustments are often necessary in HD cancer patients. These adaptations have to be carefully carried out to optimize drug exposure, ensure efficacy and reduce the risk of side-effects.
Key words: cytotoxic drugs, dosing recommendations, hemodialysis, pharmacokinetics

introduction

Since the demonstration in the 1940s that hemodialysis (HD) can sustain life and relieve the symptoms of uremia, the widespread access to dialysis that began in the 1970s has been lifesaving for patients with acute kidney failure or end-stage renal disease (ESRD). Today, >1 million people worldwide benefit from long-term dialysis. The number of patients under dialysis is increasing by at least 5% in Western countries due to increasing age and type II diabetes, the prevalence of which also increases and which is frequently associated with deterioration of renal function. Significant improvements of chronic renal replacement therapy have led to prolonged survival. Since cancer is common in the elderly, oncologists are likely to be faced with patients who suffer from both cancer and ESRD. Despite conflicting results among various studies in the 1990s, there is now sufficient evidence to conclude that there is a heightened incidence of at least some cancers in dialysis patients. Plausible mechanisms of carcinogenesis include chronic oxidative stress and compromised immune system. Patients with ESRD display enhanced genomic damage that may have pathophysiological relevance for cancer development [1]. The increased incidence of malignancies with ESRD has been discussed since the mid-70s [2–4]. In a recent study, the authors prospectively followed 454 HD patients and reported a 3-year survival rate of 65% and 12% of the deaths were due to cancer [5]. In a large cohort of Australian ESRD patients, the authors reported a higher incidence of all types of cancer in dialysis patients as compared with nondialysis pre-ESRD patients with a standardized incidence ratio of 1.35 (95% confidence interval 1.27–1.45) [6]. Ninety percent of ESRD patients undergo HD as the preferred renal replacement therapy. There is a paucity of information regarding issues surrounding the optimal management of such patients, especially those needing chemotherapy. In particular, the question of cytotoxic drug handling in those patients in terms of dosage adjustment and time of administration regarding the dialysis session needs to be addressed to optimize cytotoxic drug therapy and to minimize toxic effects in those patients.

drug handling in HD patients

In dialysis patients, two issues must be considered. First, renal function of HD patients is no longer functional. Therefore, these patients may necessitate drug dosage reduction to avoid overdosage and drug toxicity. As a result, drug prescription

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must be cautiously checked before administration=with appropriate dosage adjustment whenever necessary to ensure efficacy while avoiding overdosage and related side-effects. Secondly, drug clearance by dialysis must be taken into account for appropriate chemotherapy timing. Dialysis therapy is used in chronic uremia to remove toxic waste products that accumulate in patients with ESRD but this technique may also remove drugs. Subsequently, it is necessary to determine what fraction of drugs is removed by HD to plan chemotherapy strictly after HD sessions and thereby avoid drug removal which may result in a loss of efficacy. For drugs that are not significantly removed by dialysis, administration can be carried out anytime, before or after HD sessions. On the other hand, partial dialysis removal may also be used to improve drug tolerance. Indeed, it may be recommended to start dialysis sessions at a certain time following chemotherapy to remove the drug that has not distributed to the site of action and could generate side-effects. Such procedures have been used with some platinum for instance.

Three indices evaluate the influence of HD on drug pharmacokinetics: HD clearance, extraction coefficient and F_{HD} (dialysis extraction factor).

HD clearance is the removal rate relative to blood concentration when entering the dialyzer. It is calculated by the amount removed (mg/min) relative to the rate of presentation (mg/ml).

$$CL_{HD}(ml/min) = \frac{[(Ca - Cv) \times Qb]}{Ca},$$

with Ca, concentration entering the dialyzer (mg/ml); Cv, concentration leaving the dialyzer (mg/ml) and Qb, blood flow (ml/min).

Extraction coefficient, also called extraction ratio, is the percentage of drug removed from blood across the dialyzer. It is calculated by the rate of removal (ml/min) relative to the rate of presentation (ml/min) [7].

$$E(\%) = \frac{CL_{HD}}{Qb},$$

with CL_{HD}, hemodialysis clearance (removal; ml/min) and Qb, blood flow rate (ml/min).

Dialysis clearance and extraction coefficient measure the ability of a dialysis system to remove drug from blood. Nevertheless, they do not indicate how readily the drug is removed from the body.

Noteworthy, HD clearance and extraction ratio cannot be extrapolated to the clinical setting. It is necessary to refer to the F_{HD} of the drug (when available) to determine the clinical impact of dialysis sessions.

F_{HD} represents the influence of dialysis on drug pharmacokinetics. F_{HD} derives from the total body clearance (CL) and the HD clearance (CL_{HD}) of a drug. The influence of HD is clinically relevant if F_{HD} exceeds 25% of the overall drug elimination in a hemodialyzed patient [8]: $F_{HD} = CL_{HD}/CL$. Since F_{HD} is a quite recent concept, it is rarely reported in studies and must be calculated from CL_{HD} and CL when available. CL consists of the sum of HD clearance (CL_{HD}) and total body clearance derived from pharmacokinetic analysis of a non-HD day ($CLtot_{NHDD}$). As a result, $F_{HD} = CL_{HD}/(CL_{HD} + CLtot_{NHDD})$ [9].

most prescribed cytotoxic drugs

To our best knowledge, data remain scanty for most prescribed cytotoxic drugs in HD cancer patients. We used the list of the most prescribed cytotoxic drugs in the Insuffisance Rénale et Médicaments Anticancéreux (IRMA) population of solid tumor patients [10], where patients had decreased glomerular filtration rate (GFR) and renal insufficiency in 50%–60% of the cases. The list of the 10 most prescribed cytotoxic drugs in the IRMA study is presented in Table 1 with statements on whether dosage adjustment would be needed in ESRD patients according to two sources: the 'GPR Anticancéreux. Guide de Prescription et Rein', a prescription handbook edited in France on this topic by Launay-Vacher et al. [12] and a position paper from the International Society of Geriatric Oncology, by Lichtman et al. [11].

The literature search was carried out using PubMed and the following keyword chain: 'Drug AND ((end stage renal disease) OR dialysis OR hemodialysis)'. The term 'drug' comprised any synonyms of the International Nonproprietary Name of the drug; for instance, for 5-FU, the search was carried out on '(5FU OR 5-FU OR fluorouracile OR fluorouracil) AND ((end stage renal disease) OR dialysis OR hemodialysis)' (Table 2).

grading

Since most of the data available derive from case reports and case series, we decided to grade our recommendations for drug dosing in hemodialyzed patients, to emphasize that high-level evidence is still lacking.

Grade A—scientific evidence available on the basis of:

- randomized clinical trials with significant populations included and
- meta-analyses of clinical trials

Grade B—scientific rationale on the basis of:

- randomized clinical trials but with a weak power,
- nonrandomized clinical studies and
- cohort studies

Grade C—low level of scientific evidence:

- case–control studies,
- comparative trials with historical data,
- retrospective studies and
- case series or case reports

individual drug literature analysis

5-fluorouracil

5-Flurouracil is mostly metabolized in the liver and renal excretion of 5-fluorouracil accounts for <10% [13]. The most recent case published in the literature reports the postoperative use of 5-FU-based combination therapy in a 74-year-old patient

Table 1. Most prescribed cytotoxic drugs in the IRMA study

INN	Need for dosage adjustment in hemodialysis patients according to	
	Launay-Vacher et al. [10]	Lichtman et al. [11]
5-FU	No	No
Capecitabine	No data	No data
Carboplatin	Yes	Yes
Cisplatin	Yes	Yes
Cyclophosphamide	Yes	Not mentioned in the recommendations
Docetaxel	No data	No data
Doxorubicin	No	No data
Epirubicin	No data	No
Etoposide	Yes	Yes
Gemcitabine	No	No data
Irinotecan	No data	No data
Methotrexate	No data	No data
Oxaliplatin	No data	No data
Paclitaxel	No	No
Vinorelbine i.v.	Yes	No data

INN, International Nonproprietary Name; 5-FU, 5-fluorouracil.

Table 2. Results of the literature search

INN	Total number of references retrieved	References with abstract available
5-FU	105	90
Capecitabine	1	1
Carboplatin	58	55
Cisplatin	161	142
Cyclophosphamide	714	604
Docetaxel	14	12
Doxorubicin	157	144
Epirubicin	11	10
Etoposide	75	71
Gemcitabine	16	15
Irinotecan	9	9
Methotrexate	230	180
Oxaliplatin	4	4
Paclitaxel	81	79
Vinorelbine	2	1

Keywords chain for searching PubMed: 'Drug AND [(end stage renal disease) OR dialysis OR hemodialysis]'.
INN, International Nonproprietary Name; 5-FU, 5-fluorouracil.

with colorectal carcinoma on regular HD. The patient received weekly CPT-11 (50 mg/m^2) followed by leucovorin (10 mg/m^2) and 5-FU (400 mg/m^2) just after HD. Plasma concentrations of both SN-38, an active metabolite of CPT-11, and 5-FU were not increased compared with those of patients with normal renal function. The patient presented with grade 3 hematological toxicity that recovered by granulocyte colony-stimulating factor. The authors concluded that this 'dose-reduced Saltz regimen' is feasible for colorectal cancer (CRC) patients under dialysis [14].

5-Fluorouracil was also used in another protocol in a 68-year-old woman under dialysis. FOLFOX4 was administered with doses of oxaliplatin of 40 mg/m^2 and 5-FU of 300 mg/m^2 as a bolus and a continuous i.v. infusion of 500 mg/m^2. HD was carried out 1 h after the administration of oxaliplatin on day 1 and was repeated 2 days later after the completion of chemotherapy. Vomiting (grade 2), anorexia and leukopenia (both grade 3) were observed after the first course. A total of four courses were administered thereafter by reducing the dose of oxaliplatin to 32 mg/m^2, the i.v. bolus of 5-FU to 240 mg/m^2 and continuous infusion of 5-FU to 400 mg/m^2. Measurement of drug concentrations showed that free oxaliplatin was immediately eliminated by dialysis. The authors concluded that FOLFOX4 in dialysis patients was feasible but needed dose reduction [15].

Some data indicate that the metabolic clearance of 5-FU may be altered in patients with ESRD. Actually, uremic toxins accumulate in ESRD patients during the interdialytic period and may interfere with drug metabolism. Other authors demonstrated intact pharmacokinetics of 5-FU in one ESRD patient but impaired elimination of one 5-FU metabolite, the alpha-fluoro-beta-alanine (FBAL) between two dialysis sessions, resulting in the accumulation of FBAL. They reported that FBAL was removed by dialysis, indicating that dialysis may be effective if intolerance due to FBAL occurs [16]. Others reported the case of a 68-year-old HD patient treated with three courses of combined radiotherapy and full-dose chemotherapy with 5-FU and cisplatinum for esophageal carcinoma. Tolerance and tumor response were satisfactory without relapse at 3 years [17].

These observations indicate that 5-FU may be used at its usual dosage in patients with ESRD undergoing HD. It is however recommended to administer the drug after HD session on HD days since the drug may be removed.

capecitabine

Capecitabine and some of its active metabolites are predominantly eliminated by the kidney; 96% of the administered dose is recovered in the urine. Capecitabine is the oral inactive prodrug for 5-FU, with some particularities in the resulting distribution of 5-FU in the organism due to some specificities in the distribution of thymidine phosphorylase. This enzyme is responsible for capecitabine activation to 5-FU and other metabolites and is overexpressed in tumor cells [18, 19]. It is well known that capecitabine needs dosage adjustment in patients with renal insufficiency. In one pharmacokinetic study of capecitabine conducted on renal insufficiency patients (no HD patients), it was reported that renal impairment had no effect on the pharmacokinetics of capecitabine or 5-FU but leads to an increase in the systemic exposure to two metabolites, 5′-deoxy-5-fluorouridine (5′-DFUR) and FBAL [20]. Following administration of capecitabine, 5′-DFUR is the direct precursor of 5-FU and FBAL is the final metabolite of 5-FU. Both metabolites are not cytotoxic but the exposition to 5′-DFUR is correlated to safety. However, no data are available for patients whose GFR or creatinine clearance is <30 ml/min [10] and for HD patients.

carboplatin

Renal elimination accounts for the removal of 95% of carboplatinum. The dose administered should be adjusted in

proportion to the reduction of creatinine clearance for patients with renal impairment. Those require lower doses to achieve area under the curve (AUC) comparable with those of patients with normal renal function. Calvert et al. [21] have proposed the following formula for dose calculation: dose (mg) = AUC × (GFR + 25). In patients on chronic HD, the issue is how to evaluate the GFR in the Calvert formula. In clinical practice, an acceptable way to prescribe carboplatin in HD patients is to plan the administration after a HD session, thus during a period when the GFR is approximately equal to 0. As a result, the carboplatin dose is the same for every HD patient, i.e. equal to the target AUC × 25 [22]. Furthermore, it has been demonstrated that carboplatin was removed by HD [23]. This dialyzability may help to improve tolerance and various authors have recommended to plan HD following carboplatin infusions. In practice, it would be advisable to plan the administration of carboplatin on a nondialysis day, so that the following HD session occurs between 12 and 24 h after the course.

cisplatin

Cisplatin is mainly eliminated through the kidney (90%) [24]. Nephrotoxicity is no longer a limitation in HD patients but patients remain exposed to potential dose-related side-effects, such as anemia and neuropathy. The dose of cisplatin must therefore be reduced in HD patients. In patients on HD, cisplatin clearance is similar to that observed in patients with normal renal function after a single administration of 30 mg. However, a significant fall of the clearance of the free fraction of cisplatin has been reported in one HD patient [25]. Several studies have demonstrated good efficacy and tolerance of cisplatin in HD patients. One HD patient received four cisplatin infusions of 25 mg/m^2 in two courses and underwent HD before each treatment [26]. In another study, cisplatin was given in HD patients at a dose of 50 mg, four administrations every 15 days, followed by two administrations of 80 mg. The plasma concentration was never >3.16 μg/ml [27]. Five other HD patients received cisplatin at various doses [28]: two patients started cisplatin at the initial dose of 40 mg/m^2 followed by injections of 80 mg/m^2 and three at the dose of 80 mg/m^2 upfront. Tolerance to cisplatin in all these patients was similar to that in patients with normal renal function.

Finally, the initial doses of cisplatin in HD patients must be reduced by 50%, at a recommended dose of 25–50 mg/m^2 every 3–6 weeks [12]. Furthermore, cisplatin is highly and irreversibly bound to plasmatic proteins [24]. Free cisplatin is dialyzable and the loss of free cisplatin during HD is not compensated by bound cisplatin. Therefore, cisplatin must be given following HD sessions or on nondialysis days.

cyclophosphamide

Approximately 70%–80% of the administered dose of cyclophosphamide is transformed into metabolites by hepatic enzymes. Cyclophosphamide has at least six active metabolites, with different pharmacokinetic characteristics for each metabolite [29]. Between 30% and 60% of the total cyclophosphamide dose is eliminated by the kidneys as cyclophosphamide or metabolites [29]. All the cytotoxic effects of this drug correspond to active metabolites but most of these compounds will be inactivated thereafter. The pharmacokinetic profiles of cyclophosphamide and its metabolites can be modified in renal insufficiency patients [30, 31]. In one study, cyclophosphamide was administered at a dose of 0.5–1 g/m^2 over 1 h i.v. in HD patients (HD 7 h after administration). Mean cyclophosphamide clearance was moderately lower in HD patients than in patients with normal renal function. Furthermore, the AUC of cyclophosphamide was increased in HD patients. Consequently, it is necessary to reduce the dose of cyclophosphamide by 25% in HD patients [30].

Since cyclophosphamide is removed by dialysis, it should be given after HD sessions.

docetaxel

Docetaxel is poorly eliminated by the kidney. Only 6% of the dose administered is recovered unchanged in the urine [32]. There are limited data about the use of docetaxel in HD patients. One HD prostate cancer patient received 35 mg/m^2 of docetaxel at days 1, 8 and 15 [33]. The pharmacokinetic parameters were similar to those of patients with normal renal function. The treatment was well tolerated but the efficacy was not reported. Another cancer patient received 65 mg/m^2 of docetaxel in association with carboplatin 2 h before HD sessions. Plasma concentration of docetaxel in the HD patient was similar to those of patients with normal renal function [34]. The treatment was efficient, with grade 2 leukopenia and thrombocytopenia. Therefore, docetaxel should be used with caution in HD patients and it seems reasonable to start the treatment at a dose of 65 mg/m^2, with adaptations according to tolerance and efficacy.

Furthermore, docetaxel is not removed by the HD procedure [33], so docetaxel can be used before or after HD sessions.

doxorubicin

Doxorubicin is a first-generation anthracycline. Data on doxorubicin pharmacokinetics in patients with renal insufficiency are limited. Since doxorubicin and its main active metabolite (doxorubicinol) are not predominantly eliminated by the urinary tract [35], the dose of doxorubicin should not be modified in renal insufficiency patients in theory. Noteworthy, the AUC of doxorubicin and doxorubicinol are higher in renal insufficiency patients than in patients with normal renal function. However, the half-lives of these two compounds are the same in both patient groups [36].

Therefore, doxorubicin may not need dose adjustment in patients with renal insufficiency and in HD patients [10]. In the absence of data on the dialysance of doxorubicin and its main metabolite, the administration of doxorubicin should be done after or on a day without HD.

epirubicin

Epirubicin is a second-generation anthracycline from the same family of doxorubicin. Epirubicin is poorly eliminated by the kidney. Renal excretion is ∼9% [37].

There are limited data on the use of epirubicin in patients with ESRD and no data on epirubicin pharmacokinetics in HD patients. However, one HD patient with breast cancer received epirubicin at a weekly dose of 30 mg/m^2 for 16 weeks. The patient

had no leukopenia, thrombocytopenia or cardiotoxicity. Epirubicin was considered safe and efficient for breast cancer patients with chronic renal failure undergoing HD [38].

Finally, it does not seem necessary to modify the dose of epirubicin in HD patients. Since epirubicin removal by HD has not been studied, epirubicin should be administered after HD sessions or on nondialysis days in order to prevent unwanted drug loss.

etoposide

Approximately 40% of an etoposide dose is excreted by the kidneys [39]. Several studies have investigated the pharmacokinetics and toxicity profiles of etoposide in HD patients. Pharmacokinetic parameters were comparable to those of patients with normal renal function in two studies [28, 40]. The first consisted of a dose-escalation study of etoposide at a starting dose of 50 mg/m^2 in association with cisplatin and before HD in five patients [28]. Both drug doses were progressively increased and reached 80 mg/m^2 and 100 mg/m^2 for cisplatin and etoposide, respectively. Toxicity was manageable and the standard dose was considered feasible in HD patients. A second study carried out on one HD patient receiving etoposide in combination with doxorubicin and cyclophosphamide confirmed these findings [40]. However, other studies observed a rise of the AUC and a prolonged half-life of etoposide in renal insufficiency patients, including HD patients [22]. Additional data showed that a dose reduction of etoposide was necessary in order to avoid hematological toxicity in renal insufficiency patients [41–43].

On the basis of studies conducted in HD patients [42, 44], a dose reduction of etoposide should be recommended in HD patients. The etoposide dose should be reduced by 50% and administered at a dose of 25–75 mg/m^2/day. Finally, as etoposide is not removed by HD, etoposide can be used before or after HD sessions [42].

gemcitabine

Gemcitabine is rapidly deaminated after administration to an inactive metabolite, 2′,2′-difluorodeoxycytidine (dFdU). The renal elimination of gemcitabine and its metabolites accounts for <10% and for 90% of the administered dose, respectively [45].

The use of gemcitabine in HD patients has been found safe. Gemcitabine was given at 1000 mg/m^2 in HD pancreatic or CRC patients, on days without HD [45, 46]. Pharmacokinetic parameters (AUC, elimination half-life, C_{max}) of gemcitabine were not altered. However, a 5- to 10-fold prolongation of its elimination half-life and a higher AUC of dFdU were measured in HD patients [46]. Because dFdU may induce side-effects, it is recommended to monitor treatment tolerance while maintaining dose intensity whenever possible to preserve efficacy [46, 47].

While gemcitabine removal by HD has never been studied, it is known that dFdU is removed by HD. It is therefore recommended to start HD sessions 6–12 h after gemcitabine administration to minimize the potential side-effects of dFdU [47].

irinotecan

After administration, irinotecan is converted by carboxylesterases to an active metabolite, SN-38. Urinary excretion of irinotecan and SN-38 accounts for <20% of the elimination of the administered dose [48, 49]. The authors of two case reports emphasized the necessity for irinotecan to have its dosage reduced in ESRD patients. The first patient received irinotecan at a dosage of 180 mg/m^2 as part of a first-line folinic acid, 5-FU and irinotecan (FOLFIRI) chemotherapy for metastatic CRC and died within 3 weeks after his first course, with grade 4 diarrhea (starting day 9) and grade 4 neutropenia (starting day 14). The second patient was a 57-year-old man treated with four cycles of FOLFIRI. Febrile neutropenia occurred 10 days after the first course of irinotecan at a dosage of 180 mg/m^2 and 8 days after the second course at a reduced dose of 120 mg/m^2. The patient died of those complications. In this patient, plasma concentrations of irinotecan and its metabolite, SN-38, were measured during the course of the first FOLFIRI cycle on days 2 and 4, before and after dialysis sessions. Although irinotecan was partially dialyzable, SN-38 was not [50]. In another case report, the authors reported an efficient dose-reduced protocol with irinotecan. A 45-year-old male with chronic renal failure was diagnosed with stage 3 CRC. He received CPT-11 (50 mg/m^2, 80 mg total) weekly. No hematological or non-hematological toxicity of grade 3/4 was observed. Due to excellent tolerability and the lack of severe side-effects, the dose was increased up to 80 mg/m^2 weekly. However, dose escalation to 100 mg/m^2 resulted in severe diarrhea (grade 4). Within 2 months of treatment, the patient achieved partial remission [51].

A reduced dosage of weekly 50 mg/m^2 of irinotecan might therefore be recommended preferably after HD sessions or on nondialysis days.

methotrexate

Methotrexate is an antifolate drug exclusively eliminated via the kidney with 60%–90% of the administered drug found in the urine unchanged [52, 53]. There is no study on methotrexate pharmacokinetics in HD cancer patients. However, nine dialysis patients [54–59], including two on peritoneal dialysis and seven on HD, were treated with methotrexate for rheumatological diseases. All patients had hematological toxicity under low doses of methotrexate (2.5–10 mg/week). Seven patients recovered but three died [54, 56, 59]. Among them, one had received a single dose of 2.5 mg [54].

The use of methotrexate even at very low doses may have severe or fatal consequences in HD patients and its use is contraindicated in HD patients by the French health authorities in rheumatology. Therefore, if methotrexate is mandatory for cancer, the dose must be reduced by 75% with close monitoring of adverse reactions as long as there are no data on safety and efficacy with this dosage in HD cancer patients. Methotrexate can be removed by HD, especially when using high-flux HD membranes [60–62]. Therefore, methotrexate should be administered after HD sessions in ESRD patients.

oxaliplatin

Oxaliplatin is mainly eliminated by the kidney [63]. Its pharmacokinetic profile is altered in renal insufficiency patients. Indeed, strong correlations were found between (i) GFR and drug clearance and (ii) GFR and the AUC of the drug in patients

with various degrees of renal insufficiency [64, 65]. However, multiple administrations of oxaliplatin (130 mg/m^2 every 3 weeks) in renal insufficiency patients with a GFR > 20 ml/min/1.73 m^2 did not increase toxic effects [64]. In the same study, one ESRD patient (GFR = 13 ml/min/1.73 m^2) was excluded for sepsis after two administrations (every 3 weeks) of 60 mg/m^2. Consequently, these authors and others recommended not to modify the dosage of oxaliplatin in patients with a GFR > 20 ml/min/1.73 m^2 [64]. However, there are limited data on the pharmacokinetics and efficacy/safety of oxaliplatin in HD cancer patients. One HD patient with liver metastasis from colon cancer received hepatic arterial infusion of oxaliplatin at a dose of 60 mg twice a week during HD sessions [66]. Because the first three cycles were carried out without side-effect, the dose was escalated to 70 mg. No hematological toxicity or neuropathy was observed until the seventh cycle of treatment. However, oxaliplatin was discontinued because of tumor progression and the patient died a few months later. Other studies investigated the administration of oxaliplatin in HD patients, for which the administration of the drug was carried out before the HD session. However, these studies did not determine the optimal dose of oxaliplatin in HD patients [67].

On the basis of these limited data, it is difficult to determine whether oxalipatin can be prescribed and whether a dose reduction is necessary in HD patients. The French health authorities have contraindicated the use of oxaliplatin in HD patients.

Since the dialysis removal rate is >80% [15, 66], the administration of the drug might be best done after HD sessions or on nondialysis days [15]. Owing to the lack of convincing data on i.v. infusions, oxalipatin cannot be recommended in HD patients. However, when it is mandatory, we might indicate a starting intravenous dose of oxaliplatin reduced by 30%. oxaliplatin. However, there are no information on the efficacy and the safety of oxaliplatin in HD patients at such a dose.

paclitaxel

Paclitaxel is extensively metabolized by hepatic cytochrome *P*-450 and excreted mainly in the bile, with <10% excreted by the kidneys. Several pharmacokinetic studies of paclitaxel showed that paclitaxel pharmacokinetics in HD patients was comparable with those in patients with normal renal function [68–70]. In one study, the C_{max} and the AUC of paclitaxel at doses of 250 and 350 mg/m^2 (given on nondialysis days) were 0.450 mg/l and 14.4 mg·h/l and 0.853 mg/l and 17.9 mg·h/l, respectively. The level of systemic paclitaxel exposure in an anephric patient was comparable with (or lower than) that achieved in patients with normal renal function at a similar dosage. Furthermore, the apparent clearance in an anephric patient was within the range of that observed in patients without kidney dysfunction (273–327 versus 102–359 ml/min/m^2, respectively) [68]. In addition, several publications reported good tolerance of paclitaxel in patients with renal insufficiency [70–72]. In one case, paclitaxel was administered at the dose of 175 mg/m^2 by i.v. infusion over 24 h on a day without dialysis. Tolerance to treatment was good [73]. In another case, paclitaxel was administered at the dose of 150 mg/m^2 by i.v. infusion over 3 h in combination with carboplatin, on a day without dialysis, in a ovarian cancer HD patient. The authors reported good efficacy and tolerance [72]. In a HD ovarian cancer patient, paclitaxel was administered in three infusions of 175, 225 and 300 mg/m^2, on a day without dialysis [70]. The treatment was well tolerated and considered effective by the authors.

Therefore, paclitaxel can be used in HD cancer patients. Furthermore, since paclitaxel is not dialyzable, it may be used before or after HD sessions [68].

vinorelbine

Vinorelbine is mainly eliminated through the liver, only 8% of the administered dose being recovered unchanged from the urine [74]. There are very limited data on the use of vinorelbine in HD patients. One HD cancer patient was treated at the starting dose of 25 mg/m^2 weekly administered i.v. following HD [75]. The patient developed neutropenia and the dose was reduced by half, then re-increased to 20 mg/m^2/week with good tolerance.

Therefore, it is recommended to reduce the dose of vinorelbine in HD patients and to initiate the treatment with the starting dose of 20 mg/m^2/week i.v. There are no data on the use of oral vinorelbine in HD patients. The removal of vinorelbine by HD has not been studied, so the administration of the drug should be done after HD sessions or on nondialysis days.

discussion

Patients with end-stage kidney disease secondary to such causes as diabetes, nephroangiosclerosis, polycystic kidney disease, disorders of the urinary tract (reflux nephropathy, urolithiasis infections …) and glomerular diseases (IgA nephropathy, systemic lupus erythematosus …) among others have benefited from substantial improvements of renal replacement therapies in the last decades and have a substantially prolonged lifespan. However, chronic renal insufficiency and dialysis maintain them under a state of chronic oxidative stress which is associated with an increased risk of cancer. The management of cancer in such a population is particularly challenging. Very little is known about cytotoxic drug management in ESRD patients and even less about the optimal timing and necessary dosage adjustments depending on dialysis sessions. A lack of knowledge and data concerning the use of chemotherapy in renal insufficiency may lead to an improper use of chemotherapy and fatal toxic effects in these patients. Furthermore, the SmPC (Summary of Product Characteristics) is often insufficiently documented.

Because most cytotoxic drugs used are excreted predominantly in the urine as unchanged drug or active/toxic metabolite(s), any reduction in renal clearance may result in the accumulation of potentially toxic components and overdosage. It is also important to distinguish between drug dosage adjustment and nephrotoxicity. In HD patients, renal toxicity is no more a problem, but patients are still exposed to all other potential dose-related side-effects. The dosage of chemotherapeutic agents used in these patients will thus frequently require dosage reduction to avoid severe toxic effects. Therefore, in HD patients, careful dosage adjustment is mandatory to optimize exposure to cytotoxic drugs and to reduce the risk of adverse effects.

Table 3. Dosage adjustment recommendations for cytotoxic drugs in HD

Drug	Primary elimination pathway	Metabolites	Dosage adjustment, yes/no	Timing of administration	Recommended dose in HD	Grading of the recommendation
5-FU	Respiratory	Active	No	After HD	Standard dose	C
Capecitabine	Urinary	Active	Yes	After HD[a]	No data[a]	–
Carboplatin	Urinary	No data	Yes	After HD	Dose = AUC × (25 + 0) [21]	B
Cisplatin	Urinary	Inactive[b]	Yes	After HD	Reduction of 50%–75%	B
Cyclophosphamide	Urinary	Active and inactive	Yes	After HD	Reduction of 25%	B
Docetaxel	Faeces	Inactive	Yes	After or before HD	65 mg/m^2	C
Doxorubicin	Faeces	Active and inactive	No	After HD	Standard dose	C
Epirubicin	Faeces	Active	No	After HD	Standard dose	C
Etoposide	Faeces	Active	Yes	After or before HD	Reduction of 50%	B
Gemcitabine	Urinary	Inactive	No	6–12 h before HD	Standard dose	B
Irinotecan	Faeces	Active and inactive	Yes	After HD	No data	–
Methotrexate	Urinary	Active and inactive	Yes	After HD[a]	Reduction of 75%[a]	C
Oxaliplatin	Urinary	Active and inactive	Yes	After HD[a]	Reduction of ∼30%[a]	C
Paclitaxel	Faeces	Inactive	No	After or before HD	Standard dose	B
Vinorelbine	Faeces	Active	Yes	After HD	i.v.: Reduction of 20%–33%	C

[a]Should be avoided in HD patients.
[b]Irreversibly bound to albumin.
5-FU, 5-fluorouracil; HD, hemodialysis.

Table 4. Anticancer protocols (eight examples of frequent protocols) in HD patients

Protocol	Composition	Dosage adjustment, yes/no	Recommended doses in HD
Saltz regimen	Irinotecan (CPT-11), leucovorin, 5-FU	Yes	CPT-11: 50 mg/m^2 weekly; leucovorin: 10 mg/m^2; 5-FU: 400 mg/m^2 (after HD)
FOLFOX4	Oxaliplatin, 5-FU	Yes	Oxaliplatin: 32 mg/m^2; 5-FU: i.v. bolus 240 mg/m^2, then i.v. infusion 400 mg/m^2
FOLFIRI	Irinotecan, 5-FU	Yes	Irinotecan: 120–180 mg/m^2 resulted in two patient deaths from febrile neutropenia
FEC100	Cyclophosphamide, epirubicin, 5-FU	Yes	Cyclophosphamide: 375 mg/m^2; epirubicin: 100 mg/m^2; 5-FU: 500 mg/m^2
Carboplatin + docetaxel	Carboplatin, docetaxel	Yes	Carboplatin: Calvert, dose (mg) = AUC × (0 + 25); docetaxel: 65 mg/m^2
Cisplatin + gemcitabine	Cisplatin, gemcitabine	Yes	Cisplatin: 25 mg/m^2; gemcitabine: 1000–1250 mg/m^2
Cisplatin + docetaxel	Cisplatin, docetaxel	Yes	Cisplatin: 25 mg/m^2; docetaxel: 65 mg/m^2
Cisplatin + paclitaxel	Cisplatin, paclitaxel	Yes	Cisplatin: 25 mg/m^2; paclitaxel: 135 mg/m^2 over 24 h or 175 mg/m^2 over 3 h

5-FU, 5-fluorouracil; HD, hemodialysis.; FEC, fluorouracil, epirubicin, cyclophosphamide.

In such patients, pharmacokinetic studies are very important to measure the pharmacokinetic parameters in HD patients and to compare these data with those of patients with normal renal function.

This review provides a unique opportunity for clinicians involved in the management of dialyzed patients with cancer as it gathers all the updated information from the literature. Though mostly on the basis of small case series, it provides preliminary practical guidelines, which have been implemented in routine practice for years through a prescription handbook edited in France, the 'GPR Anticancéreux. Guide de Prescription et Rein'. This review on 15 common anticancer drugs reports that 10 of these need a dose adjustment in HD patients (Table 3). Also, the doses of most chemotherapy protocols must be adapted to renal function (Table 4). Furthermore, for two of these (capecitabine and irinotecan),

there were not enough data to recommend a specific dosage in HD patients. Most of the recommendations are on the basis of case reports or case series and were similar to another review published recently on the general topic of chemotherapy-associated renal dysfunction [75]. This underlines the need for prospective pharmacokinetic studies to assess the characteristics of cytotoxic drugs in HD patients.

conclusions

The increased incidence of malignancies in patients with chronic renal failure is now well established [2–4]. Evidence-based medicine will be increasingly necessary for cancer management in this still orphan but increasing population of patients. This review provides preliminary recommendations for dose reduction and administration timing for the most used cytotoxic drugs in HD patients. In the absence of data on a drug, it may be advisable to use any other appropriate drug for which clear dosage adjustment recommendations are available. Larger pharmacokinetic studies on cytotoxic drugs will be mandatory to provide strong evidence-based guidelines for the management of cancer in HD patients.

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disclosure

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